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EXAMINER	
GANGLE, BRIAN J	

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1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,922	PAPIEROK ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-15* is/are pending in the application.

4a) Of the above claim(s) *12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and remarks, filed 3/27/2007, are acknowledged. Claims 1-9 are cancelled. New claims 10-15 have been added. Claims 10-15 are pending.

Newly submitted claims 12-15 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the originally examined claims are drawn to a product, whereas claims 12-15 are drawn to methods of using said product. As shown by the rejections under 35 USC 102, set forth in the previous office action, there is no special technical feature linking the product and the method claims.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 12-15 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 10 and 11 are currently under examination.

Objections Withdrawn

The objection to the drawings, because they do not contain reference sign(s) mentioned in the description, is withdrawn in light of applicant's amendment to the specification.

The objection to claim 2, because the abbreviation Kda should be kDa, is withdrawn in light of the cancellation of said claim.

The objection to claims 1-4, because the term "characterized in that" is not preferred terminology in US patent applications, is withdrawn in light of the cancellation of said claims.

Objections Maintained

The objection to the disclosure, because Trypan is improperly listed as a trademark, is maintained. Trypan is not a trademarked name.

Appropriate correction is required.

Claim Rejections Withdrawn

The rejection of claims 5-7 and 9, under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101, is withdrawn. The cancellation of said claims renders the rejection moot.

The rejection of claims 1-4 and 8, under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter, is withdrawn. The cancellation of said claims renders the rejection moot.

The rejection of claim 1 as being rendered vague and indefinite by the phrase "excretion-secretion antigen" is withdrawn in light of applicant's arguments. Applicant has stated that excretion-secretion antigens are proteins found in the supernatants of a culture medium.

The rejection of claim 1 as being rendered vague and indefinite because the claim is drawn to immunoglobulins capable of lysing amastigotes and promastigotes of *Leishmania*, is withdrawn. The cancellation of said claim renders the rejection moot.

The rejection of claim 1 as being rendered vague and indefinite by the phrase "the classes IgG2 and corresponding sub-classes," is withdrawn. The cancellation of said claim renders the rejection moot.

The rejection of claim 2 as being rendered vague and indefinite by the phrase "characterized in that they are specific to the major immunogen, excreted-secreted by promastigotes or amastigotes of *Leishmania* sp., belonging to the family of the Protein Surface Antigens and corresponding to a range of molecular mass from 52 to 58 kDa," is withdrawn. The cancellation of said claim renders the rejection moot.

The rejection of claim 3 as being rendered vague and indefinite by the phrase "specific to the carboxyterminal part of the major excreted-secreted immunogen," is withdrawn. The cancellation of said claim renders the rejection moot.

The rejection of claims 4 and 8 as being generally narrative and indefinite, failing to conform with current U.S. practice, is withdrawn. The cancellation of said claims renders the rejection moot.

The rejection of claims 5-7 and 9, because they provide for the use of the immunoglobulins of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass, is withdrawn. The cancellation of said claims renders the rejection moot.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, essentially for the reasons set forth in the rejection of claims 1-4 and 8 in the previous office action.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. That the recitation of a specific epitope of a protein sequence, requiring a sequence identification, is not necessary due to the several limitations on the claimed immunoglobulins.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant has not addressed the nature of the rejection. Applicant has provided no description of the antigen to which the claimed antibodies bind. Merely stating that the claimed antibodies are specific to "a major immunogen" that is a "Protein Surface Antigen" and which corresponds to a "range of molecular mass from 52 to 58 kDa" does not describe either the antigen or the antibodies that bind to it. The need for such a description is further evidenced by applicant's disclosure that the epitope which generates the claimed antibodies does not do so in dogs that are infected by *Leishmania* sp. In addition, the claims are drawn to immunoglobulins of IgG2 and "corresponding sub-classes." In their arguments, applicant states that sub-classes are not yet known to those skilled in the art, and that specific sub-classes cannot be named. If those in the art do not know what these sub-classes are, and applicant is unable to name them, they have not been described, and applicant has not demonstrated possession of them. Moreover, applicant states that the claimed antibodies are specific to a "cryptic or immunologically silent epitope located in the carboxyterminal part of that secreted antigen." First, the "carboxyterminal part" has not been defined. Second, an "immunologically silent epitope" is an impossibility. An epitope, by definition, cannot be "immunologically silent." Without further description, one of skill in the art would not know how to generate antibodies to an epitope which does not generate antibodies. Furthermore, the composition must be able to lyse amastigotes and promastigotes of all *Leishmania* sp. *in vitro*. As stated in the 112, second paragraph rejection of the previous office action, immunoglobulins are capable of inducing pathways which lead to lysis by other molecules, such as through the activation of the complement cascade, but are not capable of directly lysing cells. Applicant has not described any antibodies that are capable of lysing cells. Applicant has also not shown that any of the claimed antibodies would have anything to do with infections by any organism other than leishmaniases.

As outlined previously, the instant claims are drawn to a composition for lysing amastigotes and promastigotes of *Leishmania* sp. *in vitro* and for neutralizing proliferation of said amastigotes and promastigotes of *Leishmania* sp., said composition comprising immunoglobulins of IgG2 and corresponding sub-classes, which are specific to the excretion-secretion antigens of promastigotes or amastigotes of *Leishmania* sp., and which are specific to a major immunogen, belonging to Protein Surface Antigens and corresponding to a range of

molecular mass from 52 to 58 kDa; wherein the immunoglobulins are specific to the carboxyterminal part of the major immunogen; wherein the immunoglobulins are specific to isotypes IgG2 in dogs and specific isotypes in other mammals, the isotypes being linked to cell-mediated immunity depending on T lymphocytes of the Th1 type; wherein the immunoglobulins are markers of immunotherapy in leishmaniases and infections by pathogenic intracellular micro-organisms in mammals.

The rejected claims are drawn to a genus of antibodies, the members of which bind to the "excretion-secretion antigens" of promastigotes or amastigotes of *Leishmania* sp. These antibodies must also have the capability to lyse said amastigotes and promastigotes and neutralize their proliferation. Dependent claims limit the genus to immunoglobulins that are specific to the major immunogen excreted-secreted by promastigotes or amastigotes of *Leishmania* sp., belonging to the family of the Protein Surface Antigens and corresponding to a range of molecular mass from 52 to 58 kDa, and to the carboxyterminal part of the major excreted-secreted immunogen.

The courts have recently decided in Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin (CAFC, 02-1187, 1/20/2004) that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See Enzo Biochem II, 323 F.3d at 965; Regents, 119 F.3d at 1568. Therefore, based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen. Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen

when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application.

In the instant application, Applicant has failed to "fully characterize" the antigen (i.e. excretion-secretion antigens) to which the claimed antibody binds. The instant claims are drawn to all immunoglobulins of the class IgG2 and corresponding subclasses with specificity to any antigen excreted or secreted by promastigotes or amastigotes of *Leishmania* sp., as long as said antibody is capable of lysing said promastigotes or amastigotes. Consequently, since Applicant has not fully characterized the antigen to which the claimed antibodies bind, the written description requirements under 35 U.S.C 112, first paragraph have not been met. To characterize an antigen, the immunoepitopes that can be found on said antigen must be identified. This characterization must not only include identification of epitopes that allow antigen:antibody binding, but also those that result in lysis of the microorganism.

The specification does not describe the excretion-secretion antigens to which the members of the claimed genus of antibodies must bind, such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. Further, the antigen to which the antibodies of claim 2 must bind is a Protein Surface Antigen, which, according to the art, is a membrane protein, and therefore cannot be excreted or secreted (see Kemp *et al.*, FEMS Immunol. Med. Microbiol., 20:209-218, 1998, IDS filed 4/29/2005).

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed.

See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

As evidenced by Greenspan et al. (Nature Biotechnology 17: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an

epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows the epitope to which any given antibody binds can only be identified empirically. Even using a competition assay, the skilled artisan cannot determine whether an antibody binds the same epitope as another antibody because an antibody that competes with another does not necessarily bind the same epitope as the other; rather, one antibody may bind a spatially overlapping epitope to sterically hinder binding of the other. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of epitopes to which the members of the claimed genus of antibodies must bind, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of antibodies. Moreover, since the specification has not identified which amino acids of the genus of epitopes to which the members of the claimed genus of antibodies must bind, which are critical or essential to the binding, one skilled in the art would not recognize that Applicant had possession of the claimed invention at the time the application was filed.

Therefore, in accordance with the *Guidelines*, the description of immunoglobulins is not deemed representative of the genus of immunoglobulins to which the claims refer.

Claims 10-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, essentially for the reasons set forth in the rejection of claims 1-4 and 8 in the previous office action

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues:

1. That the recitation of a specific epitope of a protein sequence, requiring a sequence identification, is not necessary due to the several limitations on the claimed immunoglobulins, and that the specified conditions, properties and organism are sufficient to enable one skilled in the art to produce the claimed composition.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant has not addressed the nature of the rejection. Merely stating that the claimed antibodies are specific to "a major immunogen" that is a "Protein Surface Antigen" and which corresponds to a "range of molecular mass from 52 to 58 kDa" does not provide a means by which the skilled artisan would be able to determine whether they had either the antigen or the antibodies that bind to it. This is further evidenced by applicant's claim that the epitope which generates the claimed antibodies does not do so in dogs that are infected by *Leishmania* sp. In addition, the claims are drawn to immunoglobulins of IgG2 and "corresponding sub-classes." In their arguments, applicant states that sub-classes are not yet known to those skilled in the art, and that specific sub-classes cannot be named. If those in the art do not know what these sub-classes are, and applicant is unable to name them, they would not know how to make and use them. Moreover, applicant states that the claimed antibodies are specific to a "cryptic or immunologically silent epitope located in the carboxyterminal part of that secreted antigen." First, the "carboxyterminal part" has not been defined. Second, an "immunologically silent epitope" is an impossibility. An epitope, by definition, cannot be "immunologically silent." Without further description, one of skill in the art would not know how to generate antibodies to an epitope which does not generate antibodies. Furthermore, the composition must be able to lyse amastigotes and promastigotes of all *Leishmania* sp. *in vitro*. As stated in the 112, second paragraph rejection of the previous office action, immunoglobulins are capable of inducing pathways which lead to lysis by other molecules, such as through the activation of the complement cascade, but are not capable of directly lysing cells. Applicant has not shown how to produce any antibodies that are capable of lysing cells. Applicant has also not shown that any of the claimed antibodies would have anything to do with infections by any organism other than leishmaniases. Finally, the claims encompass a composition for neutralizing proliferation of promastigotes and amastigotes of *Leishmania* sp. in any animal. As pointed out by applicant, "it is risky and dangerous to extend the results obtained in mouse and hamster for dogs." Therefore, one of skill in the art would not expect any results shown in dogs to be useful in determining efficacy in any other mammal, as encompassed by the claims.

As outlined previously, enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the

specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The instant claims are drawn to a composition for lysing amastigotes and promastigotes of *Leishmania* sp. *in vitro* and for neutralizing proliferation of said amastigotes and promastigotes of *Leishmania* sp., said composition comprising immunoglobulins of IgG2 and corresponding sub-classes, which are specific to the excretion-secretion antigens of promastigotes or amastigotes of *Leishmania* sp., and which are specific to a major immunogen, belonging to Protein Surface Antigens and corresponding to a range of molecular mass from 52 to 58 kDa; wherein the immunoglobulins are specific to the carboxyterminal part of the major immunogen; wherein the immunoglobulins are specific to isotypes IgG2 in dogs and specific isotypes in other mammals, the isotypes being linked to cell-mediated immunity depending on T lymphocytes of the Th1 type; wherein the immunoglobulins are markers of immunotherapy in leishmaniases and infections by pathogenic intracellular micro-organisms in mammals.

Breadth of the claims: The claims encompass the genus of immunoglobulins of the class IgG2 and corresponding subclasses, the members of which bind to the "excretion-secretion antigens" of promastigotes or amastigotes of *Leishmania* sp. These antibodies must also have

the capability to lyse said amastigotes and promastigotes and neutralize their proliferation. Dependent claims limit the genus to immunoglobulins that are specific to the major immunogen excreted-secreted by promastigotes or amastigotes of *Leishmania* sp., belonging to the family of the Protein Surface Antigens and corresponding to a range of molecular mass from 52 to 58 kDa, and to the carboxyterminal part of the major excreted-secreted immunogen.

Working Examples/Guidance of Specification: The specification fails to describe either the antigens or the immunoepitopes against which the claimed antibodies are raised and must subsequently bind. Nor do they disclose which immunoepitopes would result in the lysis, and consequent neutralization of the promastigotes or amastigotes of *Leishmania* sp. "Excretion-secretion antigens" are not defined, and the "major immunogen" which belongs to the family of Protein Surface Antigens is described only in that it has a mass from 52 to 58 kDa. However, Protein Surface Antigens are membrane bound proteins, which, by definition, are not excreted or secreted. Further, there is no disclosure of antibodies that are specific to Protein Surface Antigens with a mass from 52 to 58 kDa, nor is there disclosure of any antibodies capable of lysing amastigotes or promastigotes of *Leishmania* sp., let alone antibodies specific to Protein Surface Antigens with a mass from 52 to 58 kDa that are capable of binding or lysing amastigotes or promastigotes of *Leishmania* sp.

State of the Prior Art and Unpredictability of the Art: In the instant application, Applicant has failed to "fully characterize" the antigen (i.e. excretion-secretion antigens) to which the claimed antibody binds. Consequently, since Applicant has not fully characterized the antigen to which the claimed antibodies bind, the skilled artisan would not be able to make the claimed invention.

While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie *et al.* further teach that the

problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, Greenspan *et al.* (Nature Biotechnology 17: 936-937, 1999), disclose defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of a directed immune response, the specification, as filed, is not enabling.

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Deplazes *et al.* (Parasite Immunol., 17:451-458, 1995, IDS filed 4/29/2005), essentially for the reasons set forth in the rejection of claims 1-4 and 8 in the previous office action.

Applicant argues:

1. That the claims are drawn to antibodies that are specific to the carboxyterminal part of an antigen in dogs immunized with antigens of the promastigote and amastigote forms of *Leishmania infantum*. Applicant argues that the claimed antibodies are specific to an "immunologically silent epitope." Applicant contends that these antibodies do not exist in mammals that are naturally infected with *Leishmania infantum*.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant has provided no evidence that the claimed antibodies do not exist in naturally infected mammals. In fact, applicant does provide evidence that such antibodies do exist in these animals. In paragraph [0023] of the specification, applicant states, "after chemotherapy or immunotherapy, the IgG2s in dogs specific to the ES antigens of Leishmania and notably of the carboxyterminal part of PSA appear with significant improvement in the general state of dogs that have contracted *Leishmaniasis*." In paragraph [0079], applicant shows that 4 infected dogs that recovered from *Leishmania infantum* infection had IgG2 specific for the carboxyterminal part of the PSA. Because the antigen to which the claimed antibodies bind is naturally produced by *Leishmania infantum*, it would be present in animals infected by *Leishmania infantum*. Therefore, the IgG2 antibodies disclosed by Deplazes *et al.* would necessarily include the claimed antibodies.

As outlined previously, the instant claims are drawn to a composition for lysing amastigotes and promastigotes of *Leishmania* sp. *in vitro* and for neutralizing proliferation of said amastigotes and promastigotes of *Leishmania* sp., said composition comprising immunoglobulins of IgG2 and corresponding sub-classes, which are specific to the excretion-secretion antigens of promastigotes or amastigotes of *Leishmania* sp., and which are specifica to a major immunogen, belonging to Protein Surface Antigens and corresponding to a range of molecular mass from 52 to 58 kDa; wherein the immunoglobulins are specific to the carboxyterminal part of the major immunogen; wherein the immunoglobulins are specific to isotypes IgG2 in dogs and specific isotypes in other mammals, the isotypes being linked to cell-

mediated immunity depending on T lymphocytes of the Th1 type; wherein the immunoglobulins are markers of immunotherapy in leishmaniases and infections by pathogenic intracellular micro-organisms in mammals.

Deplazes *et al.* disclose IgG2 antibodies obtained from dogs that are infected with *Leishmania infantum* (see page 454, column 2, paragraph 2). Because the "excretion-secretion" antigens produced by promastigotes and amastigotes of *Leishmania* sp. are naturally produced by these organisms, a dog that is infected by *Leishmania infantum* would necessarily produce antibodies specific to the excretion-secretion antigens produced by promastigotes and amastigotes of *Leishmania* sp., including the major immunogen corresponding to a range of molecular mass from 52 to 58 kDa, and including antibodies specific to the carboxyterminal part of the major immunogen. Further, these antibodies would necessarily include antibodies having the same functional characteristics as the claimed antibodies. Finally, since the Patent Office does not have the facilities for examining and comparing Applicant's composition with the compositions of the prior art reference, the burden is upon Applicant to show a distinction between the material, structural and functional characteristics of the claimed composition and the composition of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Afrin *et al.* (Infect. Immun., 65:2371-2377, 1997), essentially for the reasons set forth in the rejection of claims 1-4 and 8 in the previous office action.

Applicant argues:

1. That the claims are drawn to antibodies that are specific to the carboxyterminal part of an antigen in dogs immunized with antigens of the promastigote and amastigote forms of *Leishmania infantum*. Applicant argues that the claimed antibodies are specific to an "immunologically silent epitope." Applicant contends that these antibodies do not exist in mammals that are naturally infected with *Leishmania infantum*.

2. That the Afrin reference describes the immune responses in hamsters and mice that are immunized with an antigenic extract of parasite alone or encapsulated in liposomes. Applicant argues that these preparations produce antibodies of any class of IgG, IgA, and IgM and

preferably induce a response of IgG1 antibodies. Applicant asserts that the claimed antibodies are specific to an antigen that is not described by Afrin.

3. That it is risky and dangerous to extend results obtained in mice and hamsters to dogs.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant has provided no evidence that the claimed antibodies do not exist in naturally infected mammals. In fact, applicant does provide evidence that such antibodies do exist in these animals. In paragraph [0023] of the specification, applicant states, "after chemotherapy or immunotherapy, the IgG2s in dogs specific to the ES antigens of *Leishmania* and notably of the carboxyterminal part of PSA appear with significant improvement in the general state of dogs that have contracted *Leishmaniasis*." In paragraph [0079], applicant shows that 4 infected dogs that recovered from *Leishmania infantum* infection had IgG2 specific for the carboxyterminal part of the PSA. Because the antigen to which the claimed antibodies bind is naturally produced by *Leishmania* sp., it would be present in animals infected by *Leishmania* sp. Therefore, the IgG2 antibodies disclosed by Afrin *et al.* would necessarily include the claimed antibodies.

Regarding argument 2, Afrin discloses animals that are infected with *Leishmania donovani*. Because the antigen to which the claimed antibodies bind is naturally produced by *Leishmania donovani*, it would be present in animals infected by *Leishmania donovani*. Therefore, the IgG2 antibodies disclosed by Afrin *et al.* would necessarily include the claimed antibodies.

Regarding argument 3, applicant's claims are not limited to dogs. The claims encompass IgG isotypes in all mammals. Neither applicant nor the art has shown any evidence that would imply that the claimed antibodies would not be produced in response to the infection of a particular mammal by *Leishmania donovani*.

As outlined previously, the instant claims are drawn to a composition for lysing amastigotes and promastigotes of *Leishmania* sp. *in vitro* and for neutralizing proliferation of said amastigotes and promastigotes of *Leishmania* sp., said composition comprising immunoglobulins of IgG2 and corresponding sub-classes, which are specific to the excretion-secretion antigens of promastigotes or amastigotes of *Leishmania* sp., and which are specifica to a major immunogen, belonging to Protein Surface Antigens and corresponding to a range of

molecular mass from 52 to 58 kDa; wherein the immunoglobulins are specific to the carboxyterminal part of the major immunogen; wherein the immunoglobulins are specific to isotypes IgG2 in dogs and specific isotypes in other mammals, the isotypes being linked to cell-mediated immunity depending on T lymphocytes of the Th1 type; wherein the immunoglobulins are markers of immunotherapy in leishmaniases and infections by pathogenic intracellular micro-organisms in mammals.

Afrin *et al.* disclose IgG2 antibodies obtained from mice that have been immunized with *Leishmania donovani* promastigote antigens, as well as from mice that are infected with *Leishmania donovani* (see page 2372, column 1, paragraph 4). Because the Protein Surface Antigens produced by promastigotes and amastigotes of *Leishmania* sp. are naturally produced by these organisms, a mouse that is immunized with *Leishmania donovani* would have produced antibodies specific to the excretion-secretion antigens produced by promastigotes and amastigotes of *Leishmania* sp., including the major immunogen corresponding to a range of molecular mass from 52 to 58 kDa, and including antibodies specific to the carboxyterminal part of the major immunogen. Further, these antibodies would necessarily include antibodies having the same functional characteristics as the claimed antibodies. Finally, since the Patent Office does not have the facilities for examining and comparing Applicant's composition with the compositions of the prior art reference, the burden is upon Applicant to show a distinction between the material, structural and functional characteristics of the claimed composition and the composition of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Sartori *et al.* (Clin. Exp. Immunol., 87:386-392, 1992), essentially for the reasons set forth in the rejection of claims 1-4 and 8 in the previous office action.

Applicant argues:

1. That the claims are drawn to antibodies that are specific to the carboxyterminal part of an antigen in dogs immunized with antigens of the promastigote and amastigote forms of *Leishmania infantum*. Applicant argues that the claimed antibodies are specific to an "immunologically silent epitope." Applicant contends that these antibodies do not exist in mammals that are naturally infected with *Leishmania infantum*.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant has provided no evidence that the claimed antibodies do not exist in naturally infected mammals. In fact, applicant does provide evidence that such antibodies do exist in these animals. In paragraph [0023] of the specification, applicant states, "after chemotherapy or immunotherapy, the IgG2s in dogs specific to the ES antigens of *Leishmania* and notably of the carboxyterminal part of PSA appear with significant improvement in the general state of dogs that have contracted *Leishmaniasis*." In paragraph [0079], applicant shows that 4 infected dogs that recovered from *Leishmania infantum* infection had IgG2 specific for the carboxyterminal part of the PSA. Because the antigen to which the claimed antibodies bind is naturally produced by *Leishmania* sp., it would be present in animals infected by *Leishmania* sp. Therefore, the IgG2 disclosed by Sartori *et al.* would necessarily include the claimed antibodies.

As outlined previously, the instant claims are drawn to a composition for lysing amastigotes and promastigotes of *Leishmania* sp. *in vitro* and for neutralizing proliferation of said amastigotes and promastigotes of *Leishmania* sp., said composition comprising immunoglobulins of IgG2 and corresponding sub-classes, which are specific to the excretion-secretion antigens of promastigotes or amastigotes of *Leishmania* sp., and which are specific to a major immunogen, belonging to Protein Surface Antigens and corresponding to a range of molecular mass from 52 to 58 kDa; wherein the immunoglobulins are specific to the carboxyterminal part of the major immunogen; wherein the immunoglobulins are specific to isotypes IgG2 in dogs and specific isotypes in other mammals, the isotypes being linked to cell-mediated immunity depending on T lymphocytes of the Th1 type; wherein the immunoglobulins are markers of immunotherapy in leishmaniases and infections by pathogenic intracellular micro-organisms in mammals.

Sartori *et al.* disclose IgG2 antibodies obtained from hamsters that have been infected with *Leishmania donovani* promastigote antigens (see page 389, column 1, paragraph 2). Because the Protein Surface Antigens produced by promastigotes and amastigotes of *Leishmania* sp. are naturally produced by these organisms, a hamster that is infected by *Leishmania donovani* would have produced antibodies specific to the excretion-secretion antigens produced by promastigotes and amastigotes of *Leishmania* sp., including the major immunogen corresponding

to a range of molecular mass from 52 to 58 kDa, and including antibodies specific to the carboxyterminal part of the major immunogen. Sartori *et al.* show that the antigens to which the hamsters have been exposed include a 52 kD antigen from *Leishmania donovani.* Further, these antibodies would necessarily include antibodies having the same functional characteristics as the claimed antibodies. Finally, since the Patent Office does not have the facilities for examining and comparing Applicant's composition with the compositions of the prior art reference, the burden is upon Applicant to show a distinction between the material, structural and functional characteristics of the claimed composition and the composition of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

New Claim Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is rendered vague and indefinite by the phrase "the classes IgG2 and corresponding sub-classes." There is no definition in the specification of the term "corresponding sub-classes." What sub-classes correspond to IgG2? Further, the use of the phrase "classes IgG2" implies that there is more than one IgG2 class. What classes are meant to be included in the claims? Applicant contends, in their arguments, that the term "classes" has been cancelled, that "sub-classes" are not yet known to those skilled in the art, and that specific sub-classes cannot be named at this time. Therefore, it appears that applicant agrees with the examiner's reasons for making this rejection. However, the terms are still present in the claim.

Claim 10 is rendered vague and indefinite by the phrase "the major excreted-secreted immunogen." What is the major immunogen? How is one to determine what the "major immunogen" is? Furthermore, how large of an immune response must be generated for a given immunogen to be considered "major"?

Claim 10 is rendered vague and indefinite by the phrase "specific to the carboxyterminal part." There is no definition provided in the specification for the term "carboxyterminal part." It is unclear what limitations are engendered by this phrase. What are the limits of the "carboxyterminal part" of the immunogen? Applicant argues, in their response, that the "carboxyterminal part" is sufficiently described in the specification to mean the last part of the protein immunogen molecule, after repeated patterns rich in leucine, as defined in prior art. The examiner has found no such description in the specification or the art, and applicant has not pointed out where this information can be found. Applicant has not provided a sequence for the putative immunogen, thus one would be unable to determine which region is "rich in leucine." Furthermore, the term "rich" is a relative term for which the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 10 is rendered vague and indefinite by the phrase "said immunoglobulins being specific to a major immunogen, belonging to Protein Surface Antigens and corresponding to a range of molecular mass from 52 to 58 kDa." It is not clear what molecule has a molecular mass from 52 to 58 kDa. It appears from the claim language that the immunglobulins are to "correspond to a range of molecular mass from 52 to 58 kDa." Furthermore, what is meant by the phrase "corresponding to a range of molecular mass from 52 to 58 kDa"? Does this mean that the molecule has a molecular mass in this range? In addition, how can one molecule have multiple masses? Additionally, the Protein Surface Antigens of *Leishmania* are membrane proteins; therefore, it is not clear how these proteins could be considered excretion-secretion antigens.

Claim 10 is rendered vague and indefinite by the phrase "said immunoglobulins being specific to isotypes IgG2 in dogs and specific isotypes in other mammals." Generally, when those of skill in the art refer to the specificity of antibodies, they are referring to the antigen to which the antibody binds. In the instant case, applicant has referred to antibodies that are specific for IgG2 isotypes. Is applicant referring to antibodies that *are* IgG2 antibodies, or to anti-idiotypic antibodies that are specific for IgG2 isotypes? Furthermore, the claim refers to "specific isotypes in other mammals." To what isotypes is applicant referring, specifically?

Claim 10 is rendered vague and indefinite because the claim is drawn to a composition of immunoglobulins capable of lysing amastigotes and promastigotes of *Leishmania*. Immunoglobulins are capable of inducing pathways which lead to lysis by other molecules, such as through the activation of the complement cascade, but are not capable of directly lysing cells.

Claim 11 is rendered vague and indefinite by the phrase "said immunoglobulins being markers for immunotherapy in leishmaniases and infections by pathogenic intracellular micro-organisms in mammals." It is not clear what is meant by the phrase "markers for immunotherapy." Does this mean that one can determine whether a given animal has received immunotherapy, or that one should provide immunotherapy for a given animal? How would one determine whether a mammal had received immunotherapy for cancer by searching for antibodies to *Leishmania* sp.?

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brian Gangle
AU 164

ROBERT A. ZEMAN
PRIMARY EXAMINER